CHALCONES AND HYDRAZONES CONTAINING 'N' AND 'S' - HETEROCYCLES: SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY STUDIES

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By

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Introduction:

Heterocyclic compounds are one of the important classes of organic compounds which have cyclic structures and contain one or more heteroatoms such as nitrogen, oxygen, sulfur, selenium or phosphorous [1,2]. Most of the naturally occurring molecules are heterocyclic compounds which act as core moiety for the biological functions of these molecules. The physical and chemical properties of heterocyclic compounds are different from the cyclic carbon rings due to the presence of heteroatoms in the ring. Heterocycles are one of the important branches of organic chemistry due to the actively involved in therapeutic agent. Heterocycles have largely contributed to the field of medicine, agriculture and to industrial sector. They have been widely used as agrochemicals, photo stabilizers, colouring agents, corrosion inhibitors, therapeutic agents, copolymers, antioxidants, etc [4-6]. They are also used as intermediates for the synthesis of organic compounds. The role of heterocycles was also observed in transition metal complexes as chiral ligands which were used as catalysts for variety of asymmetric reactions.

Heterocyclic compounds range from three to nine membered rings among which five and six membered rings are by far most important [7]. Most of the five and six membered nitrogen heterocycles are used as antimicrobial, antitubercular, anticancer, antidepressant and antidiabetic drugs [8]. Many literature reports highlighted the enhanced biological activity when there is a combination of nitrogen and sulphur heterocycles [9].

In summary, heterocyclic compounds have become prominent due to their pharmacological activities and have contributed immensely to the good of the society, in a way they have filled the limitations of natural products. Keeping in mind the prominence of heterocyclic compounds and the need to have novel compounds with better pharmacological properties, this work has been undertaken. Therefore, the work in the thesis unveils a few of the simple N and S containing heterocyclic compounds, their spectroscopic properties and biological activities.

The present work involves synthesis, characterization and biological activity evaluation of a few five and six membered nitrogen and sulphur heterocycles containing chalcone and hydrazone derivatives and the thesis has been presented in six chapters as detailed below:

Chapter 1: **Introduction to Chalcones and Hydrazones.**

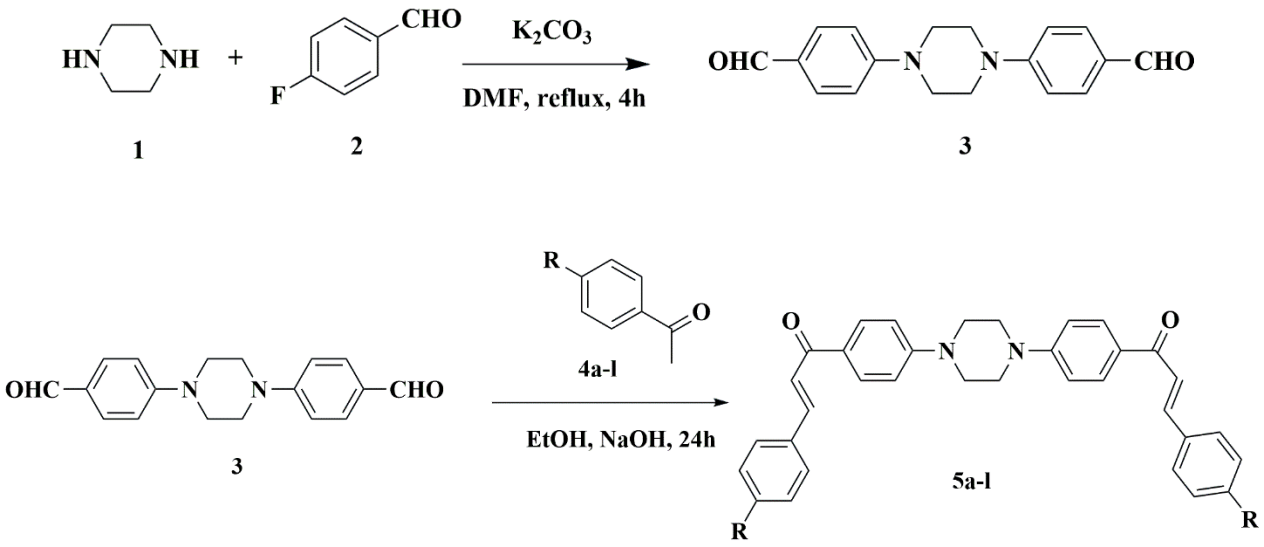
This chapter includes the brief review of literature on synthesis, reactions and biological activities of chalcone and hydrazone linked heterocycles.

Chalcone: Chalcone are simple, naturally occurring compounds and are one of the important precursors of flavonoid and isoflavonoid. Chalcone are synthesized by Claisen-Schmidt condensation of aldehydes and ketones under basic conditions [10]. Presence of α,β- unsaturated ketone in chalcone makes them biologically active possesing antimicrobial, antimalarial, anticancer, antitubercular, antidiabetic, anti-inflammatory, antidepressant, insecticidal and anti-HIV activities [11]. Many natural biologically active compounds containing chalcone moiety are Isoliquiritgenin, Butein, Cardamonin and Sapanchalcone, [12-14].

Hydrazone: Hydrazone moiety acquires a significant position in synthetic and medicinal chemistry. Hydrazones are a class of organic compounds with the structure $R_1R_2C{=}N{-}NH_2$. Hydrazone have shown to possess diverse biological and pharmacological properties such as antimicrobial, antioxidant, anticancer, antitubercular, antidiabetic and anti-inflammatory activities [15-19]. Isoniazid is the clinically approved drug containing hydrazone for the treatment of tuberculosis [18].

Chapter 2: **Synthesis, characterization and biological activities of 1,4-bis[4-(3-aryl-3-oxo)prop-1-enyl)phenyl]piperazine (5a-l)**

This Chapter describes the synthesis of 1,4-bis(4-(3-(substituted phenyl)-3-oxo)prop-1-enyl)phenyl)piperazine derivatives **(5a-l)** made by Claisen-Schmidt condensation with intermediate 4,4'-piperazine-1,4-diyldibenzaldehyde **(3)** and substituted acetophenone **(4a-l)** in the presence of ethanol and 10% NaOH by stirring for 24 h as presented in **Scheme 1**. The intermediate 4,4'-piperazine-1,4-diyldibenzaldehyde **(3)** was synthesized by reacting piperazine **(1)** with 4-fluorobenzaldehyde **(2)** in the presence of DMF and K_2CO_3 by refluxing for 4 h. The structures of the novel compounds were confirmed by FT-IR, ^{1}H-NMR, ^{13}C-NMR and ESI-Mass spectra. The synthesized compounds were screened for the *in vitro* antimicrobial activities against four bacterial strains namely *Klebsiella*, *Escherichia coli*, *Staphylococcus aureus* and *Staphylococcus mutans* and two fungal strains namely *Aspergillus niger* and *Candida albicans* using the agar disc diffusion method. Further the *in vitro* antituberculosis activities of synthesized compounds were evaluated using *Mycobacterium tuberculosis H37RV* strain using Almar Blue assay method. The *in vitro* antioxidant studies carried out by DPPH radical scavenging and nitric oxide radical scavenging models. The results of the study are discussed in detail.

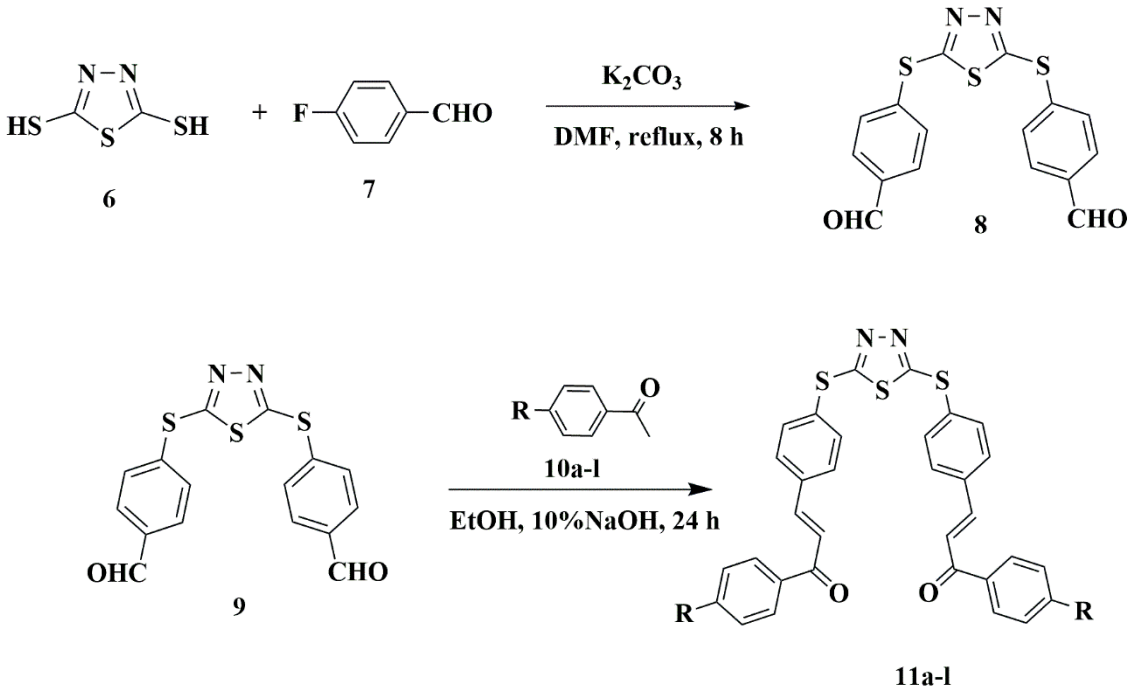


R= H, 4-Cl, 4-Br, 4-F, 4-CH_3, 4-OCH_3, 4-NO_2, 4-NH_2, 4-OH, 2,4-di OH, 3-NO_2, 2,4- di Cl.

Scheme 1: Synthetic route for 1,4-bis[4-(3-(phenyl)-3-oxo)prop-1-enyl)phenyl]piperazine (5a-l).

Chapter 3: Synthesis, characterization and biological activities of 2,5-bis[4-(3-aryl-3-oxo)prop-1-enyl)phenylthiol]-1,3,4-thiadiazole (11a-l)

This Chapter describes the synthesis of 2,5-bis[4-(3-(phenyl)-3-oxo)prop-1-enyl)phenylthiol]1,3,4-thiadiazole **(11a-l)** made by Claisen-Schmidt condensation of the intermediate 4,4'-((1,3,4-thiadiazole-2,5-diyl)bis(sulfanediyl))dibenzaldehyde **(8)** and substituted acetophenone **(9a-l)** in the presence of ethanol and 10% NaOH stirred for 24 h as presented in **Scheme 2**. The intermediate **(8)** was synthesized by reacting with 1,3,4-thiadiazole-2,5-dithiol **(6)** and 4-fluorobenzaldehyde **(7)** in the presence of DMF and K_2CO_3 by refluxing for 8 h. The structures of the novel compounds were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and ESI/MS Mass spectra. The compounds were screened *in vitro* for the antimicrobial activities of synthesized compounds tested against four bacterial strains namely *Klebsiella*, *Escherichia coli*, *Staphylococcus aureus* and *Staphylococcus mutans* and two fungal strains namely *Aspergillus niger* and *Candida albicans* using agar disc diffusion method. Further the *in vitro* antituberculosis activities of synthesized compounds are evaluated against *Mycobacterium tuberculosis H37RV* strain using Alamar Blue assay method. The *in vitro* anticancer studies were carried out against two cancer cell lines namely Hela (cervical carcinoma) and A549 (lung adenocarcinoma) using MTT assay method. The results are discussed in detail.

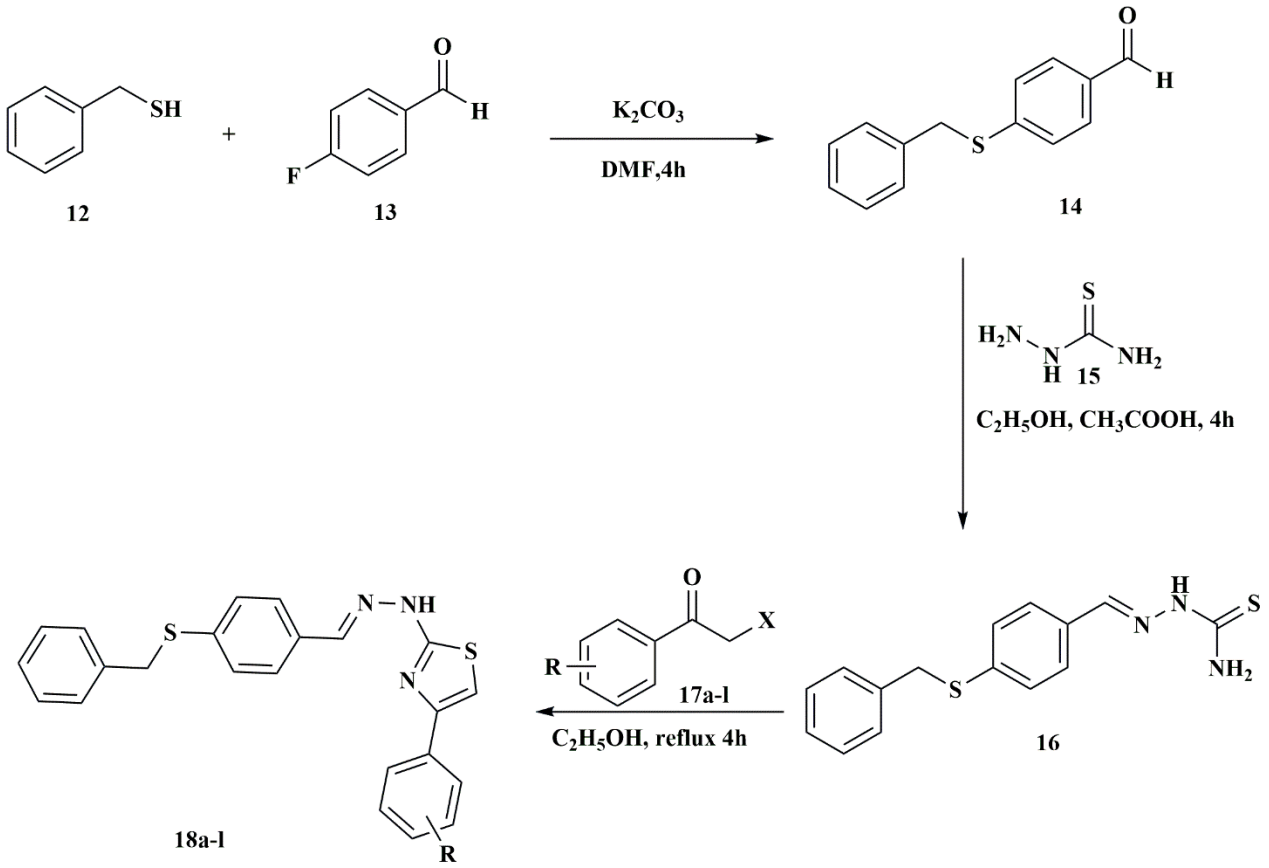


R= H, 4-Cl, 4-Br, 4-F, 4-CH_3, 4-OCH_3, 4-NO_2, 4-NH_2, 4-OH, 2,4-di OH, 2,4-di Cl, 3-OH,

Scheme 2: Synthetic route for of 2,5-bis[4-(3-(phenyl)-3-oxo)prop-1-enyl)phenylthiol]1,3,4-thiadiazole (11a-l).

Chapter 4: Synthesis, characterization and *in vivo* antidepressant activities of 2-(2-(4-(benzylthio)benzylidine)hydrazinyl)-4-arylthiazole (18a-l)

This Chapter describes the synthesis of 2-(2-(4-(benzylthio)benzylidine)hydrazinyl)-4-phenylthiazole **(18a-l)** by the reaction of α-haloacetophenone and 1-(4-(benzylthio)benzylidine)thiosemicarbazide through the Hantzsch condensation process as presented in **Scheme 3**. The key intermediates used are 4-(benzylthio)benzaldehyde **(14)** and 1-(4-(benzylthio)benzylidine)thiosemicarbazide **(16)** . The intermediate **(14)** was synthesized by reaction of phenylmethanethiol **(12)** with 4-fluorobenzaldehyde **(13)** in presence of DMF under reflux condition for 4 h as per reported procedure [19]. The intermediate **(16)** was synthesized from the reaction of 4-(benzylthio)benzaldehyde with thiosemicarbazide under acidic condition in ethanol medium.The structures of the novel compounds were confirmed by FTIR, ^{1}H NMR, ^{13}C-NMR and ESI Mass spectra. The compounds were evaluated *in vivo* for antidepressant activities by Force Swim model and Tail Suspension method and percentage change in immobility were determined. The results are discussed in detail.



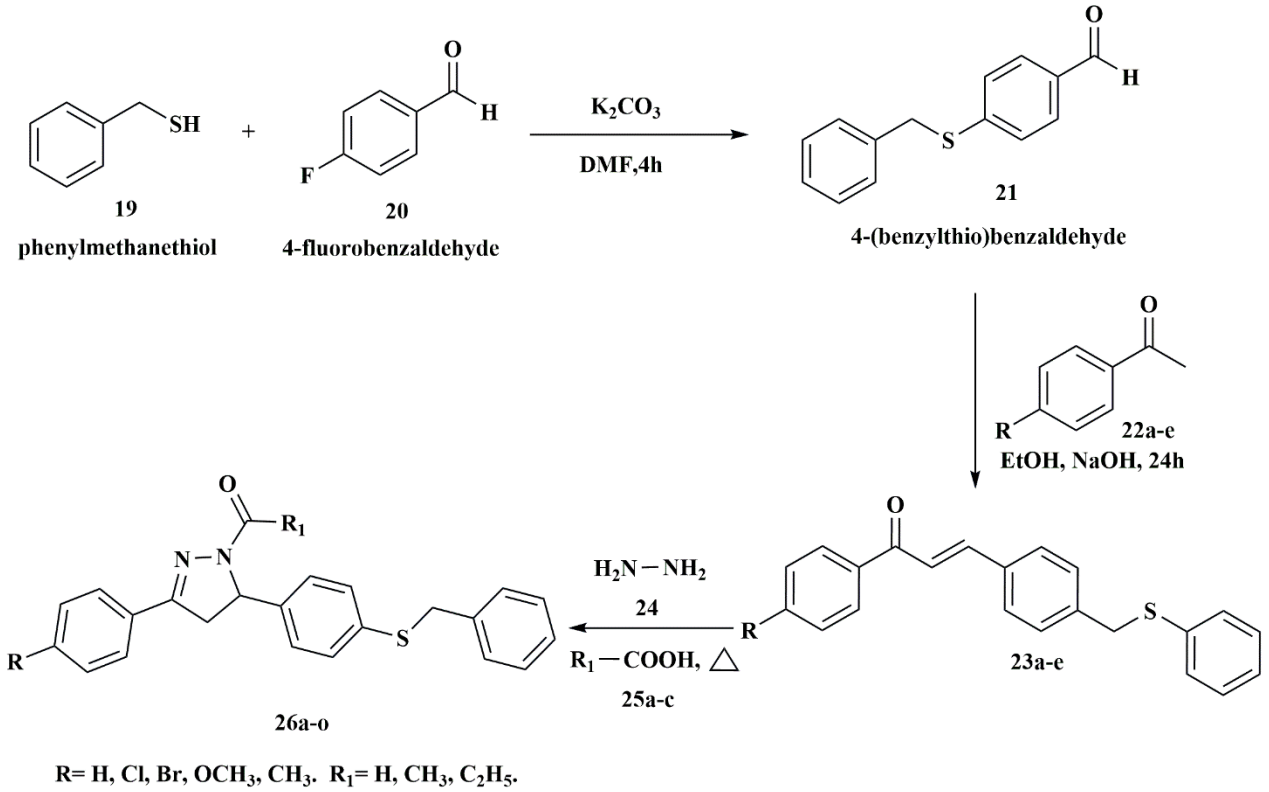
R=H, 4-Cl, 3-Cl, 4-NO_2, 4-OCH_3, 3-NO_2, 4-OCF_3, 4-CF_3, 4-F, 4-CH_3, 4-OH. X= Cl, Br

Scheme 3: Synthetic route for 2-(2-(4-(benzylthio)benzylidine)hydrazinyl)-4-arylthiazole (18a-l).

Chapter 5: Synthesis, characterization and *in vivo* antidepressant activities of 1-acyl-3-(4-(benzylthio)phenyl)-5-aryl-4,5-dihydro-1*H*-pyrazole (26a-o)

This Chapter describes the synthesis of 1-acyl-3-(4-(benzylthio)phenyl)-5-aryl-4,5-dihydro-1*H*-pyrazole **(26a-o)** from the reaction of 3-(4-(benzylthio)phenyl)-1-phenyl-prop-2-en-1-one **(23a-e)** derivatives with hydrazine hydrate in presence of formic acid, acetic acid and propionic acid respectively as presented in **Scheme 4**. 3-(4-(benzylthio)phenyl)-1-phenylprop-2-en-1-one **(23a-e)** was synthesized by Claisen Schmidt condensation of 4-(benzylthio)benzaldehyde **(21)** with acetophenone derivatives **(22a-e)** in the presence of 10% sodium hydroxide in ethanol. The 4-(benzylthio)benzaldehyde (**21**) was synthesized by reaction of phenylmethanethiol **(19)** with 4-fluorobenzaldehyde **(20)** in presence of DMF under reflux condition for 4 h as per reported

procedure [19]. The structures of the novel compounds were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and ESI Mass spectra. The compounds were screened for *in vivo* antidepressant activities using Force Swim Test **(FST)** and Tail Suspension Test **(TST)**. The results are discussed in detail.

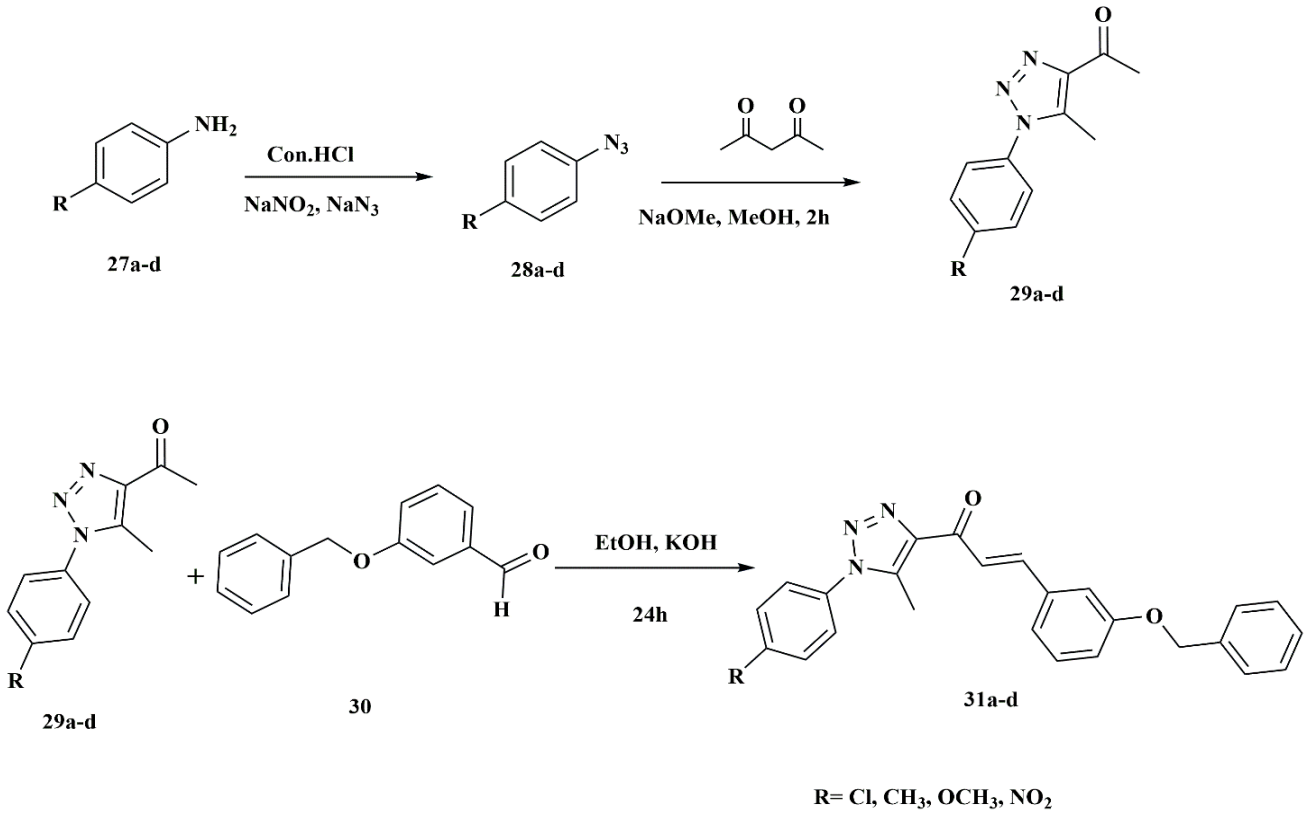


Scheme 4: Synthetic route for 1-acyl-3-(4-(benzylthio)phenyl)-5-aryl-4,5-dihydro-1H-pyrazole (26a-o).

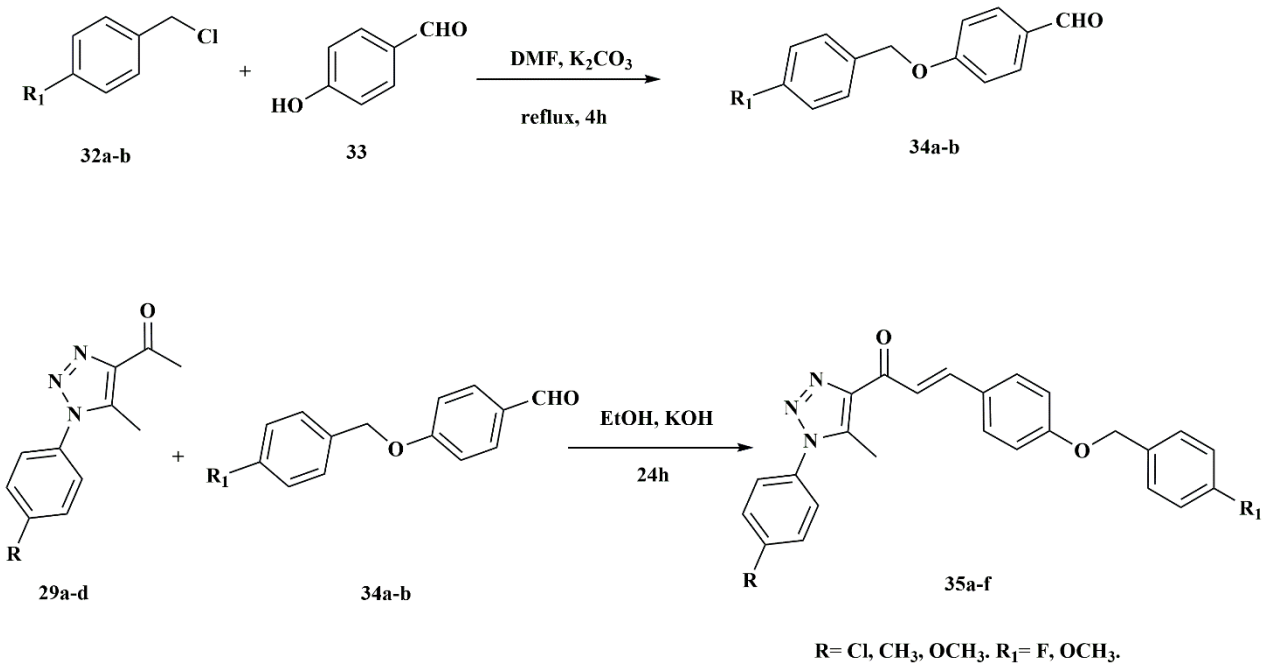
Chapter 6: Synthesis, characterization, antidiabetic, molecular docking and antioxidant activities of 3-((3/4-substituted-benzyloxy)phenyl)-1-(1-(4-substitutedphenyl)-5-methyl-1*H*-1,2,3-triazolyl)prop-2-en-1-one (31a-d, 35a-f)

This chapter describes the synthesis of 3-((3/4-substituted-benzyloxy)phenyl)-1-(1-(4-substitutedphenyl)-5-methyl-1*H*-1,2,3-triazolyl)prop-2-en-1-one **(31a-d, 35a-f)** by the Claisen-Schmidt condensation reaction of 1-(5-methyl-1-phenyl-1*H*-1,2,3-triazolyl)ethan-1-one **(29a-d)** substituted benzyloxybenzaldehyde in ethanol at room temperature as presented in **Scheme 5.1** and **5.2**. 1-(5-methyl-1-phenyl-1*H*-1,2,3-triazolyl)ethan-1-one **(29a-d)** (triazolyl ketones) was prepared by the reaction of organoazide with acetyl acetone in the presence of sodium methoxide as base and methanol as solvent. The substituted benzyloxybenzaldehydes **(34a-b)** were prepared by the methods described in the literature [20]. The formation of chalcones was confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and LCMS mass spectra.

The synthesized compounds **(31a-d, 35a-f)** were screened in vivo for their antidiabetic activity by Streptozotocin (STZ) method using Glibenclamide as the standard drug. The blood glucose levels are measured for 0, 7^{th}, 11^{th} and 15^{th} day and biochemical parameters such as blood glucose, triglycerides (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), aspartate amino transferase (AST) and alanine amino transferase (ALT) were determined. Further histopathology study of pancreas was carried out and percentage of α and β-cells were calculated by electron microscopy. Molecular docking study was performed to know the interactions between ligand and receptor and to compare the affinities of all synthesized compounds to the target protein Glucagon-Like Peptide-1 Receptor and the G-score was calculated. Further triazolyl chalcones **(31a-d,35a-f)** were tested for antioxidant properties by DPPH radical scavenging activity, nitric oxide radical scavenging activity and super oxide radical scavenging activity. The ascorbic acid was taken as the standard for comparing with synthesized compounds. The results are recorded as percentage inhibition for 5 different concentrations 10, 20, 30, 40 and 50 μg/mL and IC_{50} has been calculated. The results are discussed in detail.



Scheme 5.1: Synthetic route for 3-((3-benzyloxy)phenyl)-1-(1-(4-substitutedphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)prop-2-en-1-one (31a-d).



Scheme 5.2: Synthetic route for 3-((4-substitutedbenzyloxy)phenyl)-1-(1-(4-substitutedphenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)prop-2-en-1-one (35a-f).

Summary and conclusions

In this work, a total 61 compounds of 5 different nitrogen and sulphur heterocycles such as piperazine, 1,3,4-thiadiazole, 2,4-thiazole, 2-pyrazoline and 1,2,3-triazole linked by chalcone or hydrazone were synthesized and studied for their biological activities such as antimicrobial, anti-tuberculosis, antioxidant, anticancer, antidepressant and antidiabetic activities.

The *in vitro* antimicrobial activity study was carried out for 1,4-bis[4-(3-aryl-3oxo)prop-1-enyl)phenyl]piperazine **(5a-l)** and 2,5-bis[4-(3-aryl-3oxo)prop-1-enyl)phenylthiol]-1,3,4-thiadiazole **(11a-l)** derivatives against four bacterial strains *Klebsiella*, *Escherichia coli*, *Staphylococcus aureus* and *Staphylococcus mutans* and two fungal strains *Aspergillus niger* and *Candida albicans*.

The results have shown moderate antibacterial activity for both piperazine and 1,3,4-thiadiazole linked bis chalcones. The moderate to good activity against *Aspergillus niger* and good to excellent activity against *Candida albicans* were observed in both the series.

The good activity against *Aspergillus niger* was observed for the substituent with electron donating hydroxy group **(5i)** at para position of phenyl ring of piperazine bis-chalcone and parent 1,3,4-thiadiazole bis-chalcone **(11a)**.

The excellent activities against *Candida albicans* were observed in **5c-d** and **5h-j** series of piperazine bis-chalcone due to the presence of electronegative substituent groups such as F and Br, electron donating groups like OH and NH_2 group at para position and 2,4-di-OH of phenyl ring. The remaining derivatives of piperazine bis-chalcone have shown good activity. For 1,3,4-thiadiazole series, the excellent activities against *Candida albicans* were observed in **11d** and **11f-j** due to the presence of electron withdrawing substituent groups such as F and NO_2, electron donating groups like OCH_3, OH and NH_2 group at para position and 2,4-di-OH of phenyl ring. The remaining derivatives of piperazine bis-chalcone have shown good activity.

The *in vitro* antituberculosis activity studies carried out for 1,4-bis[4-(3-aryl-3oxo)prop-1-enyl)phenyl]piperazine **(5a-l)** and 2,5-bis[4-(3-aryl-3oxo)prop-1-enyl)phenylthiol]-1,3,4-thiadiazole **(11a-l)** derivatives screened against *Mycobacterium tuberculosis H37RV* strain using Alamar Blue assay method, indicated that Piperazine bis-chalcone, **5f** shows excellent antituberculosis activity which is comparable with Streptomycin with MIC of 6.25 µg/mL due to the presence of electron donating OCH_3 at para position of phenyl ring. **5a-b** and **5j** have shown good activity up to the concentration of 25 µg/mL due to presence of H, Cl and 2,4-di-OH at the para position of phenyl ring. The remaining derivatives show sensitivity up to the concentration of 50 µg/mL. For 1,3,4-thiadiazole, all derivatives show activity up to the concentration of 50 µg/mL. The activity appears to be due to the presence of 1,3,4-thiadiazole moiety and there was no effect of substituents on antituberculosis activity.

The *in vitro* anticancer activity study carried out for 2,5-bis[4-(3-aryl-3oxo)prop-1-enyl)phenylthiol]-1,3,4-thiadiazole **(11a-l)** derivatives against Hela (cervical carcinoma) and A549 (lung adenocarcinoma) cell lines indicate excellent anticancer activity with IC_{50} value less than 10 µg/mL. The -OH and 2,4-di-OH **(11i-j)** compounds show IC_{50} value of 20 µg/mL.

The *in vitro* antioxidant studies were carried out for 1,4-bis[4-(3-aryl-3oxo)prop-1-enyl)phenyl]piperazine **(5a-l)** indicated that all compounds showed excellent result with percentage inhibition of **59-78%** with respect to the standard, ascorbic acid.

Further triazolyl chalcones **(31a-d,35a-f)** were tested for antioxidant activity and the results indicate promising antioxidant activity for all the three models as observed in **35a-f** compared to the

standard, ascorbic acid. The presence of electron withdrawing group on para position of benzyloxy group appears to enhance the antioxidant property. Similarly, presence of electron donating group such as methoxy at para position of benzyloxy group also makes the compound exhibit good antioxidant activity in **35a** and **35c**. In the case of 3- benzyloxy substituted chalcone, highest activity was observed when electron donating substituents **(31b-c)** were present at the para position of aromatic ring. Also, presence of electron withdrawing group such as 4-nitro and 4-Cl in compounds **31a and 31d** shows good activity.

The *in vivo* antidepressant activities tested for 2-(2-(4-(benzylthio)benzylidine)hydrazinyl)-4-arylthiazole **(18a-l)** and 1-acyl-3-(4-(benzylthio)phenyl)-5-aryl-4,5-dihydro-1*H*-pyrazole **(26a-o)** derivatives have yielded excellent results with respect to standard Imipramine. The results of 1,3-thiazole substituted series of compounds reveals that the introduction of phenyl group at 4^{th} position enhances the antidepressant activity. Presence of electronegative and electron withdrawing group at para position of phenyl group increases the percentage change in immobility time in the range from **46-72%**, whereas for the standard drug Imipramine, it ranges from **64-67%**. Except **18f**, all synthesized compounds were found to be effective with respect to the standard Imipramine in FST and compounds **18a-d**, **18g**, **18j-l** show good results with respect to Imipramine in TST.

The results of *in vivo* antidepressant studies revealed that N-formyl and N-acetyl pyrazoline derivatives **(26a-j)** show excellent results . Further it was found that with increase in number of alkyl groups namely N-propionyl group, the antidepressant activity drastically decreases thereby suggesting that the higher activity is limited to formyl and acetyl substituents of pyrazoline. From the results **26b-d** and **26f-g** shows high immobility time in both the methods, where as in TST methods **26h-j** shows best result which exceed the standard Imipramine.

The in vivo antidiabetic activity measured for the series of 3 chalcones with 3-benzyloxy, 4-fluorobenzyloxy and 4-methoxybenzyloxy derivatives **31a-d, 35a-f** shows that there is a sharp decrease in the blood glucose value indicating that the targeted compounds are able to protect β cells of pancreas. From blood glucose results, compounds **31a-d** and **31b-c** shows good results related to standard. Histopathology results also shown the recovery of β- cells is around 55-70% reconfirming the above results. All compounds have significant increase in the HDL value, whereas compounds **31a**, **35a** and **35e** have grater reduction in Triglycerides and LDL value which will decreases the risk of cardiovascular diseases. All compounds have low AST and ALT values compared to the corresponding values observed in STZ induced rat before treatment. However, compound **31a-d** have the AAR value

closer to one showing the sign of prevention of the hepatocellular damage and decreased risk of cardiovascular diseases. All synthesized compounds were docked in the groove of binding site present in 3IOL and the binding free energy were calculated to be in the range of **-2.175 to -0.769 kcal/mol** related to standard Glibenclamide with binding free energy of **-6.85 kcal/mol**. Compound **31a** has the best binding energy of **-2.18 kcal/mol** with highest affinity among all the synthesized compounds. Compounds **31c** and **31d** fit into binding cleft of 3IOL receptor with G-score of **-2.17 kcal/mol** and **-2.03 kcal/mol** respectively, indicating good binding capacity supporting the experimental data related to antidiabetic activity.

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